Attorney Docket No. 5470-148CX2 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: A. Baldwin et al. Confirmation No.: 4280
Serial No.: 08/959,160 Group Art Unit: 1636
Filed: October 28, 1997 Examiner: Terry Alan McKelvey
For: *USE OF NF-KB INHIBITION IN COMBINATION THERAPY FOR CANCER*

July 20, 2004

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APPELLANT'S BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

Sir:

This Appeal Brief is filed in triplicate pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed on January 20, 2004 and received by the United States Patent and Trademark Office on January 23, 2004.

REAL PARTY IN INTEREST

The real party in interest is the University of North Carolina at Chapel Hill, the assignee of the rights to this application by virtue of assignment from the inventors recorded at the United States Patent and Trademark Office on May 14, 1998, on Reel 9189, Frame 0085.

RELATED APPEALS AND INTERFERENCES

Appellant is aware of no appeals or interferences that would be affected by the present appeal.

STATUS OF CLAIMS

Claims 1-3, 6-8, 14-16, and 29-31 are pending in the present application as of the filing date of this Appeal Brief. Appellant appeals the final rejection of these claims. As of the filing date of this Appeal Brief, all claims remain rejected under 35 U.S.C. § 103(a). A

copy of claims all pending claims as currently pending is attached hereto as an appendix **(Appendix)** presenting the claims at issue as finally rejected in the Final Official Action.

STATUS OF AMENDMENTS

A Response to first Official Action, making certain amendments to the claims, was filed on August 20, 2003. A final Official Action was mailed on November 19, 2003. A Notice of Appeal was filed on Janury 20, 2004. All amendments made by Appellant prior to submission of the present Appeal Brief are believed to have been entered.

SUMMARY OF THE INVENTION

Many cells are resistant to stimuli which are otherwise capable of inducing apoptosis, but the mechanisms involved are not fully understood. The present inventors demonstrated that anti-cancer chemotherapeutic compounds (such as daunorubicin), activate NF-κB and that this activation of NF-κB protects—undesireably—cancer cells against the cytotoxic effects of these treatments. By inhibiting NF-κB nuclear translocation, the present inventors enhanced the apoptotic killing achieved by these reagents; no such enhancement of apoptosis by NF-κB inhibitors was seen with apoptotic stimuli that do not activate NF-κB. These results and provide a method to improve the efficacy of various cancer therapies (specification; page 4 line 27 to page 5 line 5).

Proteasome inhibitors are a particularly preferred category of NF-κB inhibitors for use in carrying out the present invention (*see, e.g.,* specification; page 7 lines 4-5).

Anthracyclene antibiotics are a particularly preferred category of chemotherapeutic agent for use in carrying out the present invention (*see, e.g.,* specification; page 18, lines 7-20).

ISSUE

Whether claims 1-3, 6-8, 14-16, and 29-31 are obvious under 35 USC 103(a) over US Patent No. 5,780,454 in view of US Patent No. 6,054,467 to Gjerset.

GROUPING OF CLAIMS

For the purposes of this Appeal, with respect to the outstanding obviousness rejection, the claims are grouped as follows:

(I) Claims 1-3, 6-8, 16 and 29-31; and

(II) Claims 14-15.

Claims 1-3, 6-8, 16 and 29-31 are submitted to be patentable even if claims 14-15 are not for the additional reason discussed below.

ARGUMENT

I. Legal Standard of Obviousness

Appellant notes that a determination under 35 U.S.C. §103 that an invention would have been obvious to someone of ordinary skill in the art is a conclusion of law based on fact. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1593, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 107 S.Ct. 2187. The Patent Office has the initial burden under §103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference or combination of references must teach or suggest all the claim recitations of the present invention. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See Manual of Patent Examining Procedure* (M.P.E.P.) § 2143.

In the present case, it is respectfully submitted that the Examiner has not established a *prima facie* case of obviousness because: *(i)* there is no suggestion or motivation to combine the cited references, *(ii)* there is no reasonable expectation of success for such a combination even if such suggestion or motivation were found, and *(iii)* an element of the claimed combination is missing from the proposed combination.

II. The Rejection

Claims 1-3, 6-8, 14-16 and 29-31 stand rejected under 35 USC 103(a) as obvious over Adams et al. in view of Gjerset.

Adams et al. describe new compounds that are active as proteasome inhibitors, as NF-kB inhibitors, active for reducing the rate of degradation of p53 protein, and useful for treating cell proliferative diseases such as cancer (column 6). Among other things, Adams et al. state: **"The use of proteasome inhibitors provides a method for augmenting the expression of p53 in normal cells by preventing its degredation by the proteasome.** An example of this would be the systemic administration of proteasome inhibitor at a sufficient dose to inhibit p53 degradation by the proteasome during the treatment of the tumor with cytotoxic drugs or radiation. This will prolong and increase the levels of p53 expression in normal cells and will enhance the arrest of normal cell proliferation, **reducing their sensitivity to higher doses of radiation or cytotoxic drugs."**[1] (column 24, lines 5-15). No particular categories of "cytotoxic drugs" are identified by Adams et al. As acknowledged in the Official Action dated November 19, 2003, "Adams et al. do not specifically teach administration of an anthracyclene antibiotic such as doxorubicin as a cytotoxic drug to be administered with a proteosome inhibitor."

Gjerset concerns a combination treatment for "enhancing sensitivity to p53-mediated apoptosis" (*see, e.g.,* the title) involving *(i)* administration of p53 (or p21 or MSH-2) in combination with *(ii)* an agent that inhibits DNA repair (column 2), and *optionally* further administering a DNA damaging agent such as doxorubicin (columns 2-3). Gjerset does not teach administration of a proteasome inhibitor. Note that the p53 administered in Gjerset is an exogeneous p53, administered by means such as a p53 expression vector (see column 16, lines 52-55). Gjerset utilizes exogenous p53 because she repeatedly emphasizes that **she is concerned with cancers involving tumor cells lacking functional p53** (see, e.g., column 6, lines 5-9), as the p53 gene is "a frequent target of mutational inactivation in a wide variety of human tumors and is already documented to be the most frequently-mutated gene in common human cancers" (column 9, lines 34-38).

In short, the Gjerset teachings suggest, for the purpose of her invention, increasing p53 levels in cancer cells to **enhance cytotoxicity** thereof, while the Adams et al. teachings suggest, for the purpose of their invention, increasing p53 levels in normal cells to **reduce their sensitivity** to higher doses of cytotoxic drugs.

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[1] Independent claims 1, 6 and 14 all specify "whereby the cytotoxic effect of said chemotherapeutic agent is **increased;**" independent claims 15 and 16 both state "wherein the effect is to **increase** the cytotoxic effects of said chemotherapeutic agent."

In the Official Action of November 19, 2003, it is stated that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the cancer treatment method by proteasome inhibitor/cytotoxic drug administration taught by Adams et al. by using the cytotoxic drug doxorubicin as taught by Gjerset because Adams et al. teach that it is within the ordinary skill in the art to administer a proteasome inhibitor (which augments p53 expression by preventing degradation of p53) with a cytotoxic drug to treat cancer, including cancers encompassing breast cancer, and Gjerset teaches that it is within the ordinary skill in the art to treat cancer, such as breast cancer, by contacting animals with a composition comprising an inhibitory agent that inhibits DNA repair, and a first stimulatory agent that increases the level of p53 in said cell, and that the method may also comprise providing a DNA-damaging agent such as daunorobucin and doxorubicin in the composition." Applicants respectfully disagree.

Given that the underlying theory of Gjerset is treatment of subjects in which endogeneous p53 is mutated to inactive form by replacement with an exogenous p53, there is no reason one of ordinary skill in the art would be suggested to or motivated to administer such a patient a proteasome inhibitor suggested by Adams to reduce the rate of degredation of endogeneous p53 protein, as Gjerset is concerned with the defectiveness of the endogeneous p53 in the first instance.

Further, there could not be an expectation of success for the combination proposed in the Official Action, as Gjerset is replete with reference to the problem of mutated inactive endogeneous p53. Indeed, one skilled in the art would expect upregulation of endogeneous p53 as taught by Adams to dilute out any beneficial effect of administering an exogeneous p53 as taught by Gjerset.

As noted in connection with footnote 1 above, all independent claims of record contain provisions in the body thereof which make clear that the object of administering the proteasome inhibitor is to increase the cytotoxicity of the chemotherapeutic agent anthracyclene antibiotic. This element is absent from the teachings of Adams et al. (which in fact suggests in the opposite direction, as also noted above), and it is respectfully that this deficiency is not remedied by Gjerset.

With neither a motivation to combine the references nor a reasonable expectation of success for the proposed combination, and with an element of the claimed invention missing

from the combination of record, it is respectfully submitted that the present invention is nonobvious over Adams et al. and Gjerset, and respectfully submitted that the rejection of record should be reversed.

The present invention proceeds in a different direction from Adams or Gjerset because it is based upon a different mechanism than the mechanisms taught in either Adams or Gjerset. Indeed, an advantage of the instant invention is that it would be operable whether p53 is functional in the host subject or not.

2. Claims 1-3, 6-8, 16 and 29-31 are independently patentable as compared to claims 14-15.

Independent claim 1 states in the preamble thereof "A method of enhancing the cytotoxic effects of an antineoplastic chemotherapeutic agent." Independent claim 6 states in the preamble thereof "A method of enhancing chemotherapeutic cytotoxicity." Independent claim 16 recites in the preamble thereof "A method of increasing the cytotoxicity of a chemotherapeutic agent"

As noted above, all independent claims of record contain provisions in the body thereof which make clear that the object of administering the proteasome inhibitor is to increase the cytotoxicity of the chemotherapeutic agent anthracyclene antibiotic. Independent claims 1, 6 and 16 further reinforce this stated objective by the recitations in the preambles thereof. Language in a claim preamble acts as a claim limitation when such language serves to "give meaning to a claim and properly define the invention." *Apple Computer Inc. v. Articulate Systems Inc.,* 234 F.3d 14, 22, 57 USPQ2d 1057, 1063 (Fed. Cir. 2000). The preamble of these claims does so here, and for this additional reason it is respectfully submitted that claims 1, 6 and 16, along with claims 2-3, 7-8, and 29-31 dependent thereon, are patentable, even if claims 14-15 are not.

CONCLUSION

In light of the entire record and the above discussion, Appellant respectfully submits that claims 1-3, 6-8, 14-16, and 29-31 are patentable over the cited references. Accordingly,

Appellant respectfully requests reversal of the pending rejection of claims 1-3, 6-8, 14-16, and 29-31 and that this case be passed to issuance.

Respectfully submitted,

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TABLE OF AUTHORITIES

CASES

STATUTES

OTHER AUTHORITIES

APPENDIX

What is Claimed is:

1. (Previously presented) A method of enhancing the cytotoxic effects of an antineoplastic chemotherapeutic agent, comprising administering to a mammalian subject in need of said antineoplastic chemotherapeutic agent a therapeutically effective amount of NF-κB inhibitor in conjunction with the administration of the chemotherapeutic agent, whereby the cytotoxic effect of said chemotherapeutic agent is increased compared to that which would occur in the absence of NF-κB inhibitor,

wherein said NF-κB inhibitor is a proteasome inhibitor,

and wherein said antineoplastic chemotherapeutic agent is an anthracyclene antibiotic.

2. (Original) A method according to claim 1 wherein said NF-κB inhibitor is administered simultaneously with said chemotherapeutic agent.

3. (Previously Presented) The method of claim 1 where said chemotherapeutic agent is selected from the group consisting of daunorubicin, doxorubicin, mitoxantraone, and bisanthrene

4-5. Cancelled.

6. (previously presented) A method of enhancing chemotherapeutic cytotoxicity in a mammalian subject treated with an antineoplastic chemotherapeutic agent, comprising administering to the mammalian subject a therapeutically effective amount of an NF-κB inhibitor in conjunction with the administration of the chemotherapeutic agent, whereby the cytotoxic effect of said chemotherapeutic agent is increased compared to that which would occur in the absence of said NF-κB inhibitor,

wherein said NF-κB inhibitor is a proteasome inhibitor,

and wherein said chemotherapeutic agent is an anthracyclene antibiotic.

7. (Original) A method according to claim 6 wherein said NF-κB inhibitor is administered simultaneously with said chemotherapeutic agent.

8. (Previously Presented) A method according to claim 6 wherein said chemotherapeutic agent is selected from the group consisting of daunorubicin, doxorubicin, mitoxantraone, and bisanthrene.

9-11 Cancelled.

14. (previously presented) A method of treating a tumor in a mammalian subject with a chemotherapeutic agent, the improvement comprising administering an effective amount of an NF-κB inhibitor in conjunction with said chemotherapeutic agent, whereby the cytotoxic effect of said chemotherapeutic agent is increased compared to that which would occur in the absence of said NF-κB inhibitor,

wherein said NF-κB inhibitor is a proteasome inhibitor,

and wherein said chemotherapeutic agent is an anthracyclene antibiotic.

15. (previously presented) A method of treating a mammalian subject receiving a chemotherapeutic agent for the treatment of a neoplastic growth, the improvement comprising administering an effective amount of an NF-κB inhibitor to the subject in conjunction with said chemotherapeutic agent, wherein the effect is to increase the cytotoxic effects of said chemotherapeutic agent,

wherein said NF-κB inhibitor is a proteasome inhibitor,

and wherein said chemotherapeutic agent is an anthracyclene antibiotic.

16. (previously presented). A method of increasing the cytotoxicity of a chemotherapeutic agent administered to a mammalian subject for the treatment of a neoplastic growth, comprising administering an effective amount of an NF-κB inhibitor to said subject in conjunction with said chemotherapeutic agent, wherein the effect is to increase the cytotoxic effects of said chemotherapeutic agent,

wherein said NF-κB inhibitor is a proteasome inhibitor,

and wherein said chemotherapeutic agent is an anthracyclene antibiotic.

17-28. Cancelled.

29. (Previously Presented) The method of claim 16, wherein said chemotherapeutic agent is doxorubicin.

30. (Previously Presented) The method of claim 16, wherein said neoplastic growth is breast cancer.

31. (Previously Presented) The method of claim 16, wherein said chemotherapeutic agent is doxorubicin and said neoplastic growth is breast cancer.

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